Journal of Intellectual Disability Research

ORIGINAL ARTICLE OPEN ACCESS

Prevalence and Modifiable Risk Factors of Dementia in People With Down Syndrome: Cross-Sectional Study of Japan in Collaboration With the Intellectual Diversity for Goodness Research Consortium (INDIGO-2019)

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Received: 26 April 2025 | **Revised:** 28 November 2025 | **Accepted:** 2 December 2025

ABSTRACT

Background: People with Down syndrome (DS) have a strong genetic predisposition to Alzheimer's disease (AD). However, the clinical burden and associated risk factors in diverse, non-Western populations remain less understood. This study aimed to investigate the prevalence of dementia in Japanese adults with DS and to identify modifiable clinical factors associated with dementia.

Methods: This cross-sectional multicentre study surveyed 133 adults with DS (mean age 50.1 years) residing in 45 welfare facilities across Japan in 2019. Dementia was diagnosed by a consensus panel of physicians using established criteria (DSM-5, ICD-10, DC-LD) after comprehensive assessments, including the Japanese version of the Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQIID-J). Logistic regression analysis was performed to identify factors independently associated with dementia.

Results: Forty-six participants (34.6%) were diagnosed with dementia. The prevalence rose sharply with age: 0% in their 30s, 30.8% in their 40s, 31.6% in their 50s and 65.5% in their 60s. After adjusting for covariates, older age, female sex, dyslipidaemia and visual impairment were independently associated with dementia.

Conclusions: This study, the largest of its kind in Asia, confirms a high prevalence of dementia in institutionalized Japanese adults with DS. Crucially, this study is the first to identify dyslipidaemia and visual impairment as independent and potentially modifiable risk factors in this population. These findings highlight tangible targets for clinical interventions aimed at mitigating dementia risk in people with DS.

1 | Introduction

There are approximately 6 million people worldwide with Down syndrome (DS) (Ballard et al. 2016), most of whom have trisomy of chromosome 21 (Papavassiliou et al. 2015). DS is a genetic disorder that results in accelerated amyloid-beta accumulation in the brain via overexpression of the amyloid precursor protein gene (APP), which is one of the causative genetic forms for the early onset of familial Alzheimer's disease (Lott and Head 2019). People with DS develop amyloid plaques by age 40, and Alzheimer's disease (AD) is the main cause of their death (Fortea et al. 2021).

Most cases with DS are complicated by intellectual disability (ID) (Carr 1988). ID is characterized by deficits in both intellectual and adaptive functioning across conceptual, social and practical domains, with onset occurring during the developmental period. It is known that the lower the premorbid cognitive reserve function, the more likely people are to develop dementia in the general population (Oveisgharan et al. 2020), and it has been reported that the prevalence of dementia is higher among people with ID (Takenoshita et al. 2023). For people with DS, the low cognitive reserve due to pre-existing ID in addition to AD pathology may be another factor that contributes to the development of dementia.

In addition, factors such as possession of the apolipoprotein E (APOE)ε4 allele (Lai et al. 2020), decreased bioavailability of oestrogen (Patel et al. 2001), and concomitant epilepsy have also been reported to increase the risk of dementia in people with DS (Lott et al. 2012). Until around 1950, however, medical management of the physical complications of DS was inadequate and few cases survived to old age, and thus the number of people suffering from dementia was not high (Hartley et al. 2015). The recent increase in the average life expectancy of people with DS to about 60 years, combined with the fact that dementia occurs earlier in their life course than in the general population, has led to a skyrocketing number of people with DS affected by dementia (Bittles et al. 2007).

The prevalence of dementia in people with DS has been reported in several studies, mainly of the countries of Europe and America, but the results are inconsistent, with differences among studies. These discrepancies in study results can be attributed to variations in research methods (study populations, recruitment methods, inclusion criteria and dementia diagnostic methods). In a review by Ballard et al., more than 55% of those aged 40–49 and 77% of those aged 60–69 were reported to exhibit cognitive dysfunction (Ballard et al. 2016). Bayen et al. surveyed Medicare claims data and reported that about 20% of those aged 45–49 and 56% of those aged 60–65 with DS had dementia (Bayen et al. 2018).

In recent years, the understanding of AD in DS has been revolutionized by large-scale, international longitudinal studies from consortia such as the LonDowns Consortium, Horizon 21 and the Alzheimer's Biomarker Consortium–Down Syndrome (ABC-DS) (Maure-Blesa et al. 2025). While these projects provide deep biological insights by focusing on the presymptomatic stages of AD, the real-world clinical burden and modifiable risk factors in diverse, non-Western populations remain less understood. This cross-sectional study addresses this gap by examining dementia prevalence and its associated clinical factors in a large cohort of Japanese adults with DS residing in welfare facilities.

2 | Methods

2.1 | Ethics

This study was approved by the Internal Ethical Committee of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (1910-005) and Asahigawaso Research Institute (R1002). It was registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000038262) on 11 November 2019. The study was conducted in accordance with the ethical standards of the relevant national and institutional committees on human experimentation, the Helsinki Declaration and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. Written informed consent was obtained from participants who were deemed competent to consent after being given a full description of the study. In addition, written informed consent was obtained from legal guardians, including legally authorized representatives, of all participants.

2.2 | Participants

In October 2019, we recruited participants from facility residents in various regions of Japan. Japan is divided into three main regions (Northern, Eastern and Western Japan). In each of these three major regions, the first to fourth largest social welfare corporations in terms of the number of people in their facilities were asked to participate in the study. Our inclusion criteria were: (a) diagnosis of ID according to ICD-10 criteria (IQ < 70), (b) the presence of a caregiver (informant) who had observed the subject's living conditions for 2 years or more, (c) 20 years of age or older, and (d) diagnosis of DS (that can be verified by the facility's records).

2.3 | Assessment and Diagnosis

2.3.1 | Preliminary Check

Initially, a caregiver (informant) familiar with the participant's condition over the past 2 years completed the survey forms. The survey forms included the Japanese version of the Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQIID-J) (Deb et al. 2007; Takenoshita et al. 2020). The DSQIID-J is an established tool for assessing dementia in individuals with ID, including those with severe cases, and demonstrates excellent interrater reliability, test–retest reliability and internal consistency. Furthermore, we adopted the optimal screening threshold of 11, which has been previously established for the Japanese population (Takenoshita et al. 2020). Alongside this instrument, the survey forms collected detailed information on participants' severity of ID, educational history, medical history and activities of daily living.

2.3.2 | Screening

Two investigators (one psychiatrist and one geneticist) interviewed all caregivers (informants) of each participant to review changes in the participant's life functioning and information on the survey forms. Participants who met one of the following criteria were advanced to the next step: (a) At least one of the investigators determined that the participant had a possibility of dementia, or (b) the participant had a DSQIID-J score of 11 or higher. This two-pronged approach was designed to function as a highly sensitive

screen, ensuring that all potential cases would proceed to the comprehensive clinical examination and consensus diagnosis stage.

2.3.3 | Clinical Examination

Two research physicians (one psychiatrist and one geneticist) examined participants that were screen-positive in person. Functional changes were assessed based on DSQIID-J results. Impairments of neurocognitive domains (complex attention, executive function, learning and memory, language, perception and movement and social cognition), neurological symptoms, physical comorbidity status and severity of ID of each participant were recorded in detail.

2.3.4 | Diagnosis

The collected information (longitudinal changes of daily function and cognitive function, comorbidities, medication, life events and physiological changes with aging) was referred to and discussed by three study physicians (two psychiatrists and one geneticist). They diagnosed the presence or absence of dementia based on diagnostic criteria. In people with ID, there was a great diversity in baseline life and cognitive functions. Therefore, the decline of cognitive function or activities of daily living was considered significant when there was a clear decline from the individual's previous best level rather than a deviation from normal levels. In cases of comorbid primary psychiatric disorders such as depression, the participants were classified as having dementia if the decline in function was deemed by consensus to be unexplainable by the psychiatric disorder. The final determination was made according to the wording of each diagnostic criterion, ensuring that the decline was not better explained by other factors such as comorbid physical conditions or medication side effects.

2.4 | Diagnostic Criteria

We used three criteria in diagnosing dementia: the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) for neurocognitive disorders (American Psychiatric and American Psychiatric Association 2013), ICD-10 Research Diagnostic Criteria for dementia (World Health 1993) and Diagnostic Criteria for Psychiatric Disorders for Use with Adults with Learning Disabilities/Mental Retardation (DC-LD) for dementia (Royal College of Psychiatrists 2001). We used the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria for Alzheimer's disease dementia (ADD) (McKhann et al. 2011), the American Heart Association/American Stroke Association criteria for vascular dementia (VaD) (Gorelick et al. 2011), the 2017 Consortium on Dementia with Lewy Bodies criteria for dementia with Lewy bodies (DLB) (McKeith et al. 2017) and the International Consensus Criteria for Behavioural Variant FTD for behavioural variant frontotemporal dementia (bvFTD) (Rascovsky et al. 2011).

2.5 | Statistical Analysis

Comparisons of continuous variables between two independent groups (dementia and without dementia) were performed by independent sample t tests. Categorical variables were analysed by Pearson's χ^2 test. Binomial logistic regression analysis was performed to estimate the risk of dementia with potential predictors. The following factors were considered as potential covariates besides basic attributes (sex and age): years of education, severity of ID, visual impairment, hearing impairment, gait disturbance and the following items, which are known to have significant associations with dementia, were assessed: hypertension, dyslipidaemia, diabetes, depression, traumatic brain injury, stroke and epilepsy. Information on these comorbidities was extracted from existing medical records at the facilities and was not based on new examinations conducted for this study. Factors with $P > 0.2$ in two-group comparisons were excluded. Spearman's rank correlation test was employed to check for multicollinearity. All reported P values were two-tailed, and significance was set at $P < 0.05$. All analyses were performed using the SPSS 24.0 software program for Windows (IBM Corp., Armonk, NY, USA).

3 | Results

3.1 | Demographic

At the time the facilities were recruited to participate in the study, there were 2149 residential facilities in Japan. Some regions (Tohoku in the north and Kyushu in the west) were excluded from the study due to a heavy rain disaster in 2019. As a result, nine social welfare corporations (45 facilities in total) expressed willingness to cooperate (one from northern, four from eastern and four from western Japan).

There were 1969 adult facility residents with ID. One hundred and thirty-three (6.75%) of the 1969 had DS. Consent to participate in this study was obtained from all participants or their guardians. The survey was conducted between October 2019 and November 2020, and the data were analysed between March 2021 and June 2021. Table 1 shows the demographic details. Of the 133 participants (age range, 21–76 years; mean, 50.1 years; SD: 11.9), 46/133 (34.6%) were diagnosed with dementia (age range, 43–76 years; mean, 58.5 years; SD: 8.4). The prevalence of dementia in the participants aged 45 years and above was 45/93 (48.4%). The prevalences of dementia for each age group are shown in Table 2. Compared with the nondementia group, the dementia group had significantly more females, was older, had a shorter education duration, and had a higher DSQIID-J score. Regarding comorbidities, the dementia group had significantly more cases of visual impairment, hearing impairment, dyslipidaemia and epilepsy. The prevalence of dementia in the four corporations of western Japan was 17/59 (28.8%), while the prevalence of dementia in the five corporations of eastern and northern Japan was 29/74 (39.2%). Details of the prevalence of dementia in each age group are shown in Figure 1. All 46 dementia cases met the DSM-5 criteria. Four of the 46 cases did not meet the DC-LD and ICD-10 criteria because the pre-existing ID made assessing the presence or absence of memory impairment difficult.

3.2 | Subtypes of Dementia

Of the 46 participants with dementia, 43/46 (93.5%) were classified as having probable ADD, 1/46 (2.2%) as probable DLB,

TABLE 1 | Demographic characteristics of ID adults with DS.

	Total ($N=133$)	Dementia ($N=46$)	Without Dementia ($N=87$)	p
Age, mean years (SD)	50.1 (11.9)	58.5 (8.4)	45.7 (11.1)	<0.001*
Sex, male/female	75/58	20/26	55/32	0.029*
Education, mean years (SD)[a]	9.4 (3.7)	7.9 (4.2)	10.2 (3.2)	0.003*
Severity of ID				
Mild ID, no. (%)	0 (0)	0 (0)	0 (0)	0.794
Moderate ID, no. (%)	16 (12.0)	6 (13.0)	10 (11.5)	
Severe to profound ID, no. (%)	117 (88.0)	40 (87.0)	77 (88.5)	
DSQIID-J, mean (SD)	8.7 (11.7)	20.9 (11.5)	2.3 (4.2)	<0.001*
Comorbidity				
Visual impairment, no. (%)	23 (17.3)	17 (37.0)	6 (6.9)	<0.001*
Hearing impairment, no. (%)	25 (18.8)	15 (32.6)	10 (11.5)	0.003*
Gait disturbance, no. (%)	5 (3.8)	3 (6.5)	2 (2.3)	0.223
Hypertension, no. (%)	3 (2.3)	1 (2.2)	2 (2.3)	0.963
Dyslipidaemias, no. (%)	28 (21.1)	15 (32.6)	13 (14.9)	0.017*
Diabetes, no. (%)	6 (4.5)	3 (6.5)	3 (3.4)	0.417
Depression, no. (%)	1 (0.8)	0 (0)	1 (1.1)	0.465
Traumatic brain injury, no. (%)	1 (0.8)	0 (0)	1 (1.1)	0.465
Stroke, no. (%)	1 (0.8)	0 (0)	1 (1.1)	0.465
Epilepsy, no. (%)	32 (24.1)	17 (37.0)	15 (17.2)	0.011*

Note: p value is a comparison of those with and without dementia.
Abbreviations: DSQIID-J, the Japanese version of the Dementia Screening Questionnaire for Individuals with Intellectual Disabilities; ID, Intellectual Disabilities; SD, standard deviation.
[a]For 125/133 (94.0%), the duration of education was confirmed. Subject with missing data were excluded from the analysis.
*Significant differences.

TABLE 2 | Prevalence of dementia in each age group.

Age	Dementia (N)	Total (N)	Dementia (%)
20–24	0	3	0
25–29	0	6	0
30–34	0	4	0
35–39	0	11	0
40–44	1	16	6.25
45–49	11	23	47.8
50–54	3	20	15.0
55–59	9	18	50.0
60–64	9	15	60.0
65–69	10	14	71.4
70–74	2	2	100.0
75–79	1	1	100.0

2/46 (4.3%) as possible ADD and possible DLB, and there was no case classified as bvFTD. This classification was based on the application of specific clinical criteria (e.g., NIA-AA) by a consensus panel, which utilized the symptom profile gathered from the DSQIID-J and all other available clinical information, rather than the DSQIID-J score.

3.3 | Potential Predictors of Dementia

Comparisons of the dementia and non-dementia groups by potential predictors such as comorbidities are shown in Table 1. The potential predictors of dementia were examined by logistic regression analysis. Among the variables, age and years of education showed a high association with a Spearman coefficient $|r|=0.70$. Therefore, the analysis was conducted in two models, using one of the two variables (age or years of education) in which collinearity was confirmed. Table 3 shows the results of binary logistic regression analyses using diagnosis of dementia as an objective variable. In Model 1, the covariates used were age, sex, dyslipidaemia, visual impairment, hearing impairment and epilepsy. A significant association was found between dementia and two variables: age (OR 1.124; 95% CI 1.124–1.192, $p<0.001$) and dyslipidaemia (OR 4.023; 95% CI 1.334–12.132, $p=0.013$). In Model 2, the covariates used were years of education, sex, dyslipidaemia, visual impairment, hearing impairment and epilepsy. A significant association was found between dementia and three variables: female sex (OR 2.492;

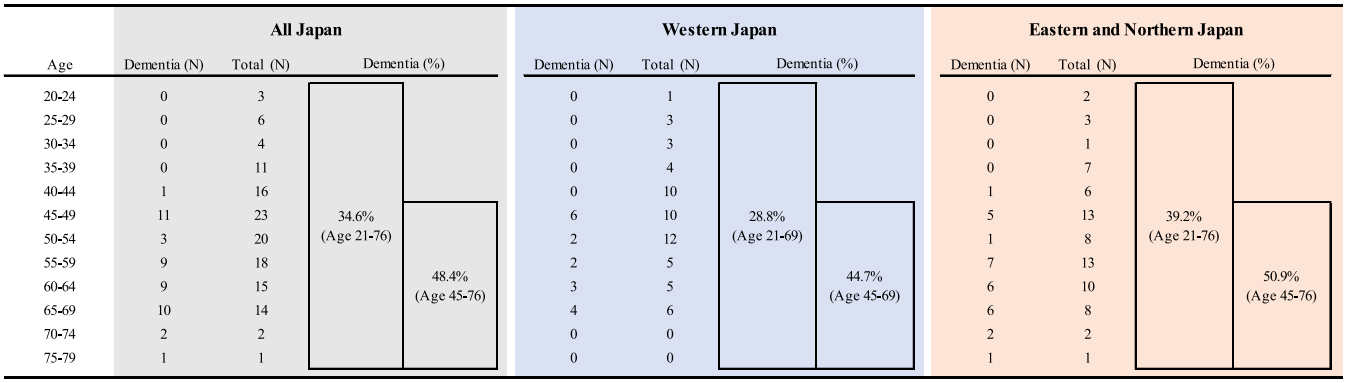

FIGURE 1 | Prevalence of dementia for each age group in each area of Japan studied.

TABLE 3 | Models predicting the probability of dementia in people with DS.

Model 1	Odds ratio (95% CI)	*p*	Beta coefficient
Age, per year	1.124 (1.061–1.192)	<0.001*	0.117
Sex, female	2.383 (0.942–6.030)	0.067	0.868
Dyslipidaemia	4.023 (1.334–12.132)	0.013*	1.392
Visual impairment	2.557 (0.697–9.383)	0.157	0.939
Hearing impairment	1.842 (0.507–6.690)	0.354	0.611
Epilepsy	1.487 (0.525–4.217)	0.455	0.397
Model 2	**Odds ratio (95% CI)**	***p***	**Beta coefficient**
Years of education, per year[a]	0.901 (0.791–1.026)	0.114	−0.105
Sex, female	2.492 (1.045–5.940)	0.039*	0.913
Dyslipidaemia	3.444 (1.258–9.430)	0.016*	1.237
Visual impairment	3.659 (1.052–12.730)	0.041*	1.297
Hearing impairment	2.292 (0.689–7.620)	0.176	0.829
Epilepsy	2.301 (0.847–6.245)	0.102	0.833

Abbreviation: 95% CI, 95% confidence interval.
[a]For 125/133 (94.0%), the duration of education was confirmed. Subject with missing data were excluded from the analysis.
*Significant differences.

95% CI 1.045–5.940, $p=0.039$), dyslipidaemia (OR 3.444; 95% CI 1.258–9.430, $p=0.016$) and visual impairment (OR 3.659; 95% CI 1.052–12.730, $p=0.041$).

3.4 | Dementia and Cognitive Reserve Function (Pre-Existing ID and Education)

This study consisted of individuals requiring institutional care, with severe to profound ID accounting for 88.0% and moderate ID for 12.0%. Consequently, no individuals with mild ID were included in this sample. The difference in the severity of ID between the participants with dementia and those without dementia was not significant. The duration of education was confirmed in 125 (94.0%) of 133 participants. The dementia group had significantly fewer years of education than the non-dementia group (mean, 7.9 years; SD: 4.3 vs. mean, 10.2 years; SD: 3.2; $p=0.003$).

4 | Discussion

As the largest study of dementia in DS in Asia, our research investigated a Japanese cohort with a distinct genetic and lifestyle profile compared with Western populations. Our findings confirm that the high prevalence of dementia in people with DS is a universal phenomenon that transcends these differences, underscoring the powerful influence of the underlying genetic mechanisms.

4.1 | Comparison of Dementia Prevalence With Previous Studies

The prevalence of dementia in people with DS reported in previous studies varies widely. For example, when comparisons were restricted to those 45 years and older, Coppus et al. (2006) reported a dementia prevalence of 16.8% (85/506), Bayen et al. (2018) reported 40.2% (353/878), and this study reported 48.4% (45/93). One possible factor contributing to the differences in prevalence studies is the effect of study design, including survey methodology and sample selection. Methodologically, our study employed a direct assessment approach like that of Coppus et al., whereas Bayen et al.'s research utilized health insurance claims data. Moreover, we focused exclusively on institutionalized individuals, whereas earlier research included both institutionalized and community-dwelling populations. Further, studies of dementia in populations with ID yielded different results depending on how dementia was defined and which diagnostic criteria were used (Silverman et al. 2013). Our previous cross-sectional study conducted on people with ID without DS reported that more severe ID is associated with an increased risk of dementia (Takenoshita et al. 2023). Coppus et al. (2006)

reported that 29.6% of their participants had severe to profound ID (Coppus et al. 2006), while Bayen et al. did not report the severity (Bayen et al. 2018). In contrast, the majority of participants in this study (88.0%) had severe to profound ID. Greater heterogeneity in lifestyle is observed among individuals with milder ID, and this diversity introduces a greater potential for confounding factors when investigating the association between the severity of ID and dementia. The subjects in this study, however, were primarily institutionalized individuals with severe to profound ID, leading to a more uniform lifestyle. While this sample homogeneity limits the generalizability of our results, it also serves to minimize the impact of such confounding variables. It is well known that the risk of dementia increases with a lower cognitive reserve, and the severity of ID may affect the prevalence of dementia in the group studied. Differences in the severity of ID among study participants may also be responsible for the differences in the results between studies.

4.2 | Potential Risk Factors for Dementia in Down Syndrome: Dyslipidaemia and Visual Impairment

The significant finding of this study is the strong association between dementia and dyslipidaemia in individuals with DS. Although individuals with DS are known to be prone to lipid metabolism abnormalities (Gastelum Guerrero et al. 2024), our study is the first to identify dyslipidaemia as a potential independent risk factor for dementia in this population. Because dyslipidaemia is a treatable condition, intervention such as routine monitoring, tailored dietary changes (e.g., controlling saturated fat intake) and targeted pharmacotherapy (e.g., statins) under clinical guidance holds the potential to be a realistic and promising approach for reducing the risk of developing dementia in people with DS. The association may be mediated by APOE gene polymorphism, as the APOEε4 allele is a known cause of dyslipidaemia (Dallongeville et al. 1992). Compared with a community-based study reported by Bayen et al. (2018), the prevalence of dyslipidaemia in our cohort was nearly equivalent (21.5% vs. 21.9%) despite significantly lower rates of hypertension (3.2% vs. 22.3%) and diabetes (4.3% vs. 11.5%) (Table S1). The low prevalence of these latter conditions is likely attributable to the managed diets and lifestyles of the facility residents. Similarly, this study is the first to report a link between visual impairment and dementia in people with DS. People with DS have a high frequency of ophthalmic complications that increase with age (Bull et al. 2022). Although our cross-sectional study cannot determine causality, visual impairment should be considered a potential risk factor for dementia. Within the context of the rapidly advancing field of DS-AD research, our results complement the biomarker literature by highlighting modifiable, late-life clinical factors that may affect the transition to symptomatic dementia. For instance, while biomarkers indicate who is on the AD trajectory, our findings on factors like dyslipidaemia point to interventions that could potentially modify the timing or severity of clinical onset.

4.3 | Association of Education Duration With Dementia Risk in People With DS

A longer duration of education and ongoing intellectual engagement are reportedly associated with a reduced risk of dementia in the general population (Oveisgharan et al. 2020; Amieva et al. 2014). However, it remains unclear whether this protective effect applies to individuals with DS, in whom genetic factors and accelerated aging have profound influences. We previously reported that the duration of education may have a protective effect against dementia in people with ID without DS (Takenoshita et al. 2023). In the present study, however, the final logistic regression analysis showed no significant association between education duration and dementia. The absence of a significant association suggests that the potent effects of genetics and accelerated aging in DS may overwhelm any modest protective effect from education. Alternatively, it is possible that, because the majority of our cohort had severe to profound ID, they may have been unable to benefit from the protective effects of education to the same extent as those with milder forms of ID or without ID. Finally, our study may have lacked sufficient statistical power to detect such an effect. Therefore, the role of education and cognitive reserve in the trajectory of dementia for people with DS remains an open question, highlighting the urgent need for large-scale, longitudinal studies.

4.4 | Potential Factors Contributing to Regional Differences in Prevalence

A notable finding of our study was the regional difference in dementia prevalence, with a higher rate observed in eastern and northern Japan (39.2%) compared with western Japan (28.8%). However, this observation must be interpreted with caution, as it may be attributable to confounding variables within our sample rather than a true regional disparity. For instance, unexamined differences in the distribution of participant age or the severity of ID between the regional cohorts could account for the observed variance. Although our cross-sectional study was not designed to investigate these causal factors, plausible external factors—such as regional variations in diet (e.g., salt intake), environment or historical disparities in special education—warrant future investigation. These external hypotheses, however, remain speculative and should be considered secondary to the more probable explanation of sample imbalance. This finding underscores the need for future prospective studies to clarify the true impact of both participant-level and regional variables on dementia risk in this population.

4.5 | Limitations

First, participation was limited to facility residents, most of whom had severe to profound ID. This may differ from the actual conditions of people with DS living in the community. Second, we utilized observer-rated scales rather than objective cognitive tests to assess dementia. This methodological choice was primarily driven by the limitations of our cross-sectional design. Diagnosing dementia requires evidence of cognitive decline from a previous baseline, which cannot be captured by objective cognitive tests administered at a single time point. Therefore, we opted for observer-rated scales that can evaluate functional changes over time, a decision also supported by anticipated floor effects in our cohort with severe to profound ID. This approach, however, may have lacked the sensitivity to identify early or mild dementia, potentially underestimating its prevalence. Third,

information about the presence or absence of complications was collected from personal information that had already been recorded at the facility. Because they were not reevaluated in this study, the exact number of complications may deviate from the actual number. For instance, for comorbidities like visual and hearing impairments, we could not consistently obtain granular data on the specific diagnosis, severity or correction status, which limits a deeper interpretation of these findings. Fourth, because this is a cross-sectional study and it is unclear whether the factors shown to be associated with dementia are attributable to dementia or are risk factors for dementia, it is not possible to conclude a causal relationship. Fifth, the study's design and diagnostic criteria were based on standards from 2019. We utilized the ICD-10 diagnostic criteria, which has since been superseded by the ICD-11. Furthermore, our study relied on clinical assessment without the use of advanced fluid or imaging biomarkers, which are now central to the diagnostic and prognostic frameworks used by international research consortia. This limits the direct comparability of our diagnosed cases with biomarker-defined stages of AD and represents a significant limitation of our study in the context of the current research landscape.

5 | Conclusions

This study, the largest of its kind in Asia, confirmed a high prevalence of dementia in a Japanese cohort of adults with DS. A further strength of this study is the successful inclusion of many individuals with severe to profound ID, a group frequently excluded from large international DS cohort studies. The study is the first to identify two independent and potentially modifiable risk factors: dyslipidaemia and visual impairment. This discovery provides tangible targets for clinical intervention in this high-risk population. However, these findings must be interpreted within the context of our cohort, which consisted exclusively of institutionalized adults who typically have a higher severity of ID. Therefore, validating these findings in community-based cohorts with a broader spectrum of ID and lifestyle diversity is a critical next step.

Acknowledgements

We acknowledge the staff of the Intellectual Diversity for Goodness Research Consortium (INDIGO-2019), which consists of eight corporations (42 facilities in total): Social Welfare Corporation Yuaikai; Ibaraki Social Welfare Corporation Asunaronosato; Chiba Social Welfare Corporation Kouseienn; Independent Administrative Institution, the National Center for Persons With Severe Intellectual Disabilities, Nozominosono; Social Welfare Corporation Harunago; Social Welfare Corporation Soujukai; Social Welfare Corporation Aiikukai; and Social Welfare Corporation Asahigawaso, for managing the investigation. We also thank the Hyogo Social Welfare Corporation for its participation in the survey. We sincerely thank Ms. Yifei Tang and Ms. Rutsu Matsuzaki for their skilful assistance and data management.

Funding

This study was supported by the Nippon Foundation (R.K., grant number 2018488269) and JSPS KAKENHI (S.Ta., grant number 21 K15713). The funders had no role in the design and conduct of the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Prevalence of comorbidities by age group and demographic details.